16. (twice amended) The method of claim 15 further comprising predicting the prognosis of the patient based on the reactivity of the patient sample with [the] different peptides.

Please cancel claims 17-20.

Remarks

Applicant Dr. John Harley and the undersigned greatly appreciated the opportunity to discuss this case with the Examiner and supervisory Examiner Thomas Cunningham on August 9, 1994. To review briefly, Dr. Harley explained how as a physician he is actively treating many patients suffering from a variety of autoimmune disorders and that the assays currently used to diagnosis these patients are limited. It is generally believed by those working in this field that diagnostic tests which were more specific, i.e., allowing one to accurately diagnosis not just that autoantibodies were present but also which antigens there were autoantibodies directed against as well as to how many epitopes, would greatly increase the physician's ability to predict a patient's long term prognosis and plan appropriate treatments.

Dr. Harley also briefly explained what is generally known about autoimmune disorders, especially systemic lupus erythematosus (SLE). This disorder primarily affects young adult women and can be a debilitating and even fatal disease. Patients vary widely in the titer (quantity) and specificity of

autoantibodies, which may be reactive against DNA, RNA, nucleoproteins, or other proteins. Examples of antigens to which autoantibodies are directed against that have been identified include Ro/SSA, La/SSB, Sm antigens (snRNP containing U1, U2, U4/U6 and U5 RNA). These are all discussed in more detail in the background of the invention at pages 1 to 4 of the application.

One of the Examiner's concerns that was discussed was why the claimed peptides were useful. Dr. Harley explained that since the pattern of autoantibodies which are present in a patient changes over the course of the disease and certain autoantibodies are associated with more severe complications than others (such as kidney failure and congenital heart block in infants born to mothers with anti-La/SSB and anti-Ro/SSA autoantiboides), it is extremely useful for physicians to have access to more definitive assays. The currently available assays use material which is usually isolated from natural sources; as the Examiner is well aware, this seldom yields completely pure material and is expensive and time consuming to make. Recombinant antigens are available for a few of the autoantibodies, where the DNA encoding the antigen has been sequenced, but these are few in number and also require relatively expensive and time consuming purification procedures.

The claimed peptides offer two advantages for use in assays for physicians: it is a great deal faster, easier and

cheaper to make short peptides rather than proteins having a molecular weight in excess of 40,000 Daltons and one can define the specificity to a **portion of the autoantigen**, rather than merely to the entire autoantigen. As Dr. Harley explained, it has now been determined, solely as a result of studies conducted with overlapping octapeptides (i.e., as described in the application, peptides consisting of amino acids 1-8, 2-9, 3-10, etc.) that the number of epitopes on a particular protein which are immunoreactive with autoantibodies **increases** as the disease progresses, allowing one for the first time to assess the rate of progression of the disease. **None of the prior art assays can be used for this purpose.**

Since the data demonstrating efficacy in the treatment of patients using the assays is not currently available, although data showing the usefulness of the peptides in assays as discussed above is shown in the application, applicant has agreed to cancel the claims to methods of treatment of patients, without prejudice, in order to facilitate allowance of the claims.

Copies of the publications referred to by Dr. Harley at the interview are enclosed:

R. Hal Scofield and John B. Harley, "Autoantigenicity of Ro/SSA antigen is related to a nucleocapsid protein of vesicular stomatitis virus" Proc. Natl. Acad. Sci. USA 88, 3343-3347 (April 1991)

Scofield, et al., "A Common Autoepitope near the Carboxyl Terminus of the 60-kD Ro Ribonucleoprotein: Sequence Similarity with a Viral Protein" J. Clin. Immunol. 11(6), 378-388 (1991)

J.A. James and John B. Harley, "Linear Epitope Mapping of an Sm B/B' Polypeptide" J. Immunol. 148(7), 2074-2079 (1992)

K. L. Hardgrave, et al., "Antibodies to Vesicular Stamatitis Virus Proteins in Patients with Systemic Lupus Erythematosus and in Normal Subjects" Arthritis Rheumatism 36(7), 962-970 (1993)

J. A. James, et al., "Basic Amino Acids Predominate in the Sequential Autoantigenic Determinants of the Small Nuclear 70 K Ribonucleoprotein" Scand. J. Immunol. 39, 557-566 (1994)

Huang, et al., "Human Anti-Ro Autoantibodies Bind Peptides Accessible to the Surface of the Native Ro Autoantigen" submitted to Scan. J. Immunol. 8/94

Venrooij and Gelder "B Cell Epitopes on Nuclear Autoantigens" Arthritis & Rheumatism 37(5), 608-616 (May 1994), (particular attention is drawn to the first column on page 608 which details the usefulness of the assays using standard antigen-antibody reaction in the diagnosis and treatment of patients with autoimmune disease)

Insertion of Trademark ™

The Examiner is authorized to capitalize any trademark. Generic terminology, *where known*, has been inserted. There is no legal requirement that trademarks be in capital letters nor that generic terminology be used in all cases if not known.

Amendment of Title

The title has been amended to reflect that the claimed reagents are peptides.

Election of Species

Applicants affirm again their election of species as to the amended claims. It is understood, however, that the restriction requirement has been withdrawn and that all claims are therefore pending until a final determination that no generic claim is allowable over the prior art. The non-elected species other than Ro/SSA have been cancelled from the claims solely to facilitate allowance of claims at this time, reserving the right the prosecute the cancelled subject matter without prejudice in divisional or continuation applications.

Obviousness Type Double Patenting

As previously agreed, an appropriate Terminal Disclaimer with U.S.S.N. 07/648,205 is enclosed.

Rejections under 35 U.S.C. §112

Applicant appreciates the withdrawal of many of the rejections of claims 1-3 and 7-20 under §112, second paragraph.

Claims 1-3 and 7-20 were again rejected under 35 U.S.C. §112 as indefinite on the basis that the reference in the following claims should be to peptide, not peptides. This has been corrected in the amended claims.

Rejection under 35 U.S.C. §101

Claims 1-3 and 7-20 were rejected under 35 U.S.C. §101 on the basis that applicants have not conclusively demonstrated the specificity of the peptide reaction with autoantibodies (utility in diagnosis) or *in vivo* utility as a therapeutic or vaccine.

As noted above, the claims to methods for treatment have been cancelled to facilitate prosecution of the claims drawn to peptide reagents and assays using the reagents.

The utility of these peptides is clearly demonstrated in the application, as discussed at the interview and summarized above. See, in particular, the data in Table 2 showing that the peptides react with very high specificity to naturally occurring autoantibodies, and page 12, last paragraph, and page 24, describing the reactions with specific patient sera.

Rejections under 35 U.S.C. §112

The specification has been objected to and claims 1-3 and 7-20 rejected under 35 U.S.C. §112, second paragraph, on the basis of non-enablement. These rejections are respectfully traversed if applied to the amended claims.

The claims to pharmaceutical use have been cancelled solely to facilitate prosecution of the present application.

The application details in the background of the invention the incidence of autoantibodies reactive with specific antigens as described by the scientific literature. The correlation between the presence of autoantibodies and disease has been established for decades. The claimed peptides were identified by reaction with autoantibodies isolated from patients diagnosed with autoimmune disease. Those peptides which were not immunoreactive were not claimed. *A priori*, the claimed peptides must react with patient sera containing autoantibodies. Moreover, the data (referred to above) provided in the application demonstrate that the peptides do **not** react with antibodies in normal sera (which, by definition, means it does not contain autoantibodies).

The Examiner's attention is drawn to the specification as follows:

correlation between autoantibody and disease: pages 2 to 3 and cited literature, copies of which have been submitted to the examiner in the Information Disclosure Statement; page 15, last paragraph

selectivity of binding to peptides by autoantibodies in antisera characterized by standard clinical definitions: page

12, first paragraph; page 13, second and third paragraphs; page 21, third paragraph

how to subtract background absorbance from assays using binding of peptides to autoantibodies: last paragraph of page 12; page 16, last paragraph

reproducibility of results with multiple patients: page 15, first paragraph

deletion and substitution studies with claimed peptides showing only six amino acids required for binding: page 25, third paragraph; page 26; page 28, last paragraph

A copy of the summary of the binding data which was shown by Dr. Harley at the interview is also enclosed.

In summary, the peptides are useful because they are reactive only with the autoantibodies present in sera; if the autoantibodies are not present, the peptides do not react with the sera; if there is a reaction, the patient must have autoantibodies.

With respect to length, the Examiner is again reminded that the peptides are derived from the full length protein (in the case of Ro/SSA, some 52,000, 54,000, or 60,000 Daltons in size, considerably longer than the claimed 40 amino acids!). Since the full length protein is reactive with the autoantibodies, one would predict that the autoantibodies would also be reactive with a forty amino acid peptide including the

claimed octapeptide to which binding **has been experimentally demonstrated.**

Rejections under 35 U.S.C. §103

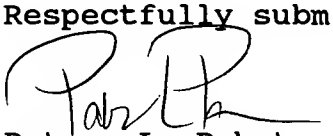
Applicant greatly appreciates the withdrawal of all of the prior art rejections.

Inventorship

As discussed with the Examiner, enclosed is the executed Declaration of Dr. R. Hal Scofield stating that he is not an inventor of the claimed subject matter of the present application.

Claims 6-9 and 17-20 have been cancelled. Allowance of all claims 1-5 and 10-16, as amended, is earnestly solicited.

Respectfully submitted,



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U.S. SERIAL NO: 07/867, 819
FILED: April 13, 1992
AMENDMENT

CERTIFICATE OF MAILING UNDER 37 CFR §1.8a

I hereby certify that this paper, along with any paper referred to as being attached or enclosed, is being deposited with the United States Postal Service on the date shown below with sufficient postage as first-class mail in an envelope addressed to the Commissioner of Patents and Trademarks, Washington, D.C. 20231.

Date: September 27, 1994

Patricia Hilger